

MDT

Questions *and* Answers

Revised 1996

Action Programme for the Elimination of Leprosy
World Health Organization



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Questions

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Answers

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FOREWORD

Since the production of the booklet "MDT Questions and Answers" in 1991, the outlook towards leprosy has changed dramatically. This change and the opportunity to conquer leprosy as from the public health point of view led WHO to pass a resolution, at its forty-fourth World Health Assembly, on the goal of the elimination of leprosy as a public health problem by the year 2000. This goal has created a new awareness and enthusiasm in most endemic countries.*

Multidrug therapy (MDT) will be the main tool used by national programmes to achieve their elimination goals. The widescale implementation of MDT has brought about major changes in treating patients in practically all national programmes. The WHO Study Group on Chemotherapy of Leprosy (TRS 847, 1994) reviewed the experiences gained on MDT and made recommendations to further simplify and improve MDT services.

In the light of the recommendations made by the Study Group and the diverse feedback received on the original document, WHO's Action Programme for the Elimination of Leprosy felt that this booklet should be revised. It is hoped that this revision will meet the needs of field personnel involved in leprosy elimination. The Action Programme would appreciate receiving relevant comments and suggestions to improve it further.

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*Action Programme for the Elimination of Leprosy
WHO, Geneva, 1996*

* WHO/CTD/LEP/91.3

QUESTIONS AND ANSWERS ON MDT

Q.1

Is WHO-recommended multidrug therapy (MDT) the best combination available for treatment of multibacillary (MB) and paucibacillary (PB) leprosy in leprosy control today?

A: *Yes, it is the best combination available today, as proved by its successful application in leprosy control under varying conditions since 1982. The combination not only cures leprosy but is also highly cost-effective.*

As of today, there is no confirmed case of MDT resistance anywhere in the world. In addition, re-treatment with the WHO-MDT regimen has been effective in all cases of relapses.

Q.2

What is the evidence that WHO-MDT is effective in MB and PB leprosy?

A: *The most important indicator for the effectiveness of a chemotherapeutic regimen is the rate of occurrence of relapse following successful completion of the scheduled course of treatment. The information available with the Action Programme for the Elimination of Leprosy, WHO, from a number of control programmes shows that the relapse rate is very low (0.1% per year for PB and 0.06% per year for MB on the average). In addition, the low frequency of side-effects has made it highly acceptable to patients in a variety of settings.*

Can MDT prevent the resistance of M. leprae to anti-leprosy drugs?

A: Yes, it can. It is estimated that an advanced, untreated lepromatous leprosy patient harbours about 10^{11} or 11 logs live organisms. Out of these, the proportion of naturally-occurring drug-resistant mutants is estimated to be 1 in 7 logs for rifampicin; 1 in 6 logs each for dapsone and clofazimine. The organisms resistant to one drug will be susceptible to the other drugs in MDT as their mechanisms of action are different. For example, in a population of 11 logs M. leprae, 4 logs or 10 000 M. leprae will be naturally resistant to rifampicin. These organisms will not be killed by rifampicin, but will be killed by dapsone and/or clofazimine. Clofazimine being a repository drug, i.e. it is stored in the body after administration and is then slowly excreted, it can be given as a loading dose as 300 mg once a month. This will ensure that the optimal amount of clofazimine is present in the body tissue, even if the patient occasionally misses his or her daily dose.

As of today, there is no confirmed case of MDT resistance anywhere in the world. In addition, re-treatment with the WHO-MDT regimen has been effective in all cases of relapses.

Why is rifampicin given only once a month?

A: Rifampicin is an exceptionally potent bactericidal agent against M. leprae. A single dose of 600 mg is capable of killing 99.9% or more of viable organisms. However, the rate of killing is not proportionately enhanced by subsequent doses. It is also possible that rifampicin exerts a delayed antibiotic effect for several days, during which the organism is incapable of multiplying. The high bactericidal activity of rifampicin makes a once a month application of the drug feasible and cost-effective for leprosy control programmes.

Some programmes are using modified MDT regimens; are these acceptable?

A: The WHO-recommended regimens are optimal regimens, and any modification which strengthens these regimens is acceptable, as long as the additional costs are affordable. However, three main considerations should be taken into account:

- a) rifampicin should be one of the components of MDT;*
- b) rifampicin 600 mg should be given at least once a month to all patients; and*
- c) at least two anti-leprosy drugs should be used in the MB regimen and one anti-leprosy drug should be used in the PB regimen, in addition to rifampicin, in order to prevent the occurrence of rifampicin-resistant M. leprae.*

At present WHO-MDT is the main regimen used by national programmes in all endemic countries. The Study Group recommended that there should be no changes in the composition or doses of the drug, nor in the "rhythm" (i.e. frequency and duration) of therapy.

Q.6

Can MDT eliminate persisting M. leprae?

A: *The persisting M. leprae are, by definition, those viable organisms which are fully susceptible to the drugs but are surviving despite adequate treatment with anti-leprosy drugs, probably because they are in a low or dormant metabolic state. So far we do not have a drug which can kill these persisting organisms, although rifampicin is known to be capable of killing persisting organisms in another mycobacterial disease, tuberculosis. The evidence so far accumulated showed that persisters, even if they exist, do not play an important role in the occurrence of relapses in leprosy among patients treated with MDT.*

Q.7

Is there any evidence that the drugs included in MDT can antagonize each other's antibacterial activity?

A: *All experimental and clinical evidence indicates that there is no antagonism among the drugs included in MDT. The experience with MDT so far has shown the combination to be the most effective.*

What is the reason for giving MDT to MB patients for two years and to PB patients for six months?

A: The most important component of the MDT regimens is rifampicin. The frequency of naturally-occurring mutants, resistant to rifampicin, is 1 in 7 logs. The majority of rifampicin-susceptible M. leprae are killed by the monthly doses of rifampicin, but in MB it probably takes two years for daily doses of dapsone and/or clofazimine to eliminate all rifampicin-resistant mutants, these being weakly bactericidal agents. This is a very conservative estimate and in reality it may take less time. In PB patients six months of rifampicin by itself should be satisfactory, theoretically, to kill all the organisms. However, dapsone has been added in order to avoid rifampicin resistance in patients who are wrongly classified as PB.

Is it necessary to give MDT to PB patients until clinical inactivity is achieved?

A: *No, it is not necessary to give MDT to PB patients until clinical inactivity. PB patients can be cured in 6 months with the WHO-MDT regimen. It should be recognized that clinical activity in PB leprosy does not necessarily imply direct correlation with bacterial multiplication. In a large proportion of patients it is not possible to achieve clinical inactivity in six months even though all the organisms are killed. The evidence from the follow-up of PB patients in THEMYS-supported field trials of MDT shows that the lesions become inactive gradually over a period of one to two years after the treatment has been discontinued. The occurrence of relapses in PB patients is very low and, as yet, there is no established relationship between disease activity status at the time of completing treatment and subsequent relapses. However, it is important that the initial classification of patients designated as having paucibacillary leprosy is accurate.*

Q.10

What is meant by fixed duration treatment for MB and PB patients?

A: *Fixed duration treatment for MB patients means that after taking 24 monthly doses of MDT this patient is cured and should be discharged from the register. Similarly, for PB patients, after taking 6 monthly doses of MDT this patient is cured and should be discharged.*

Q.11

Is it necessary to give MDT to MB patients until skin smear negativity?

A: *No. Available information suggests that 24 doses of MDT are sufficient to cure an MB patient. There is no need to continue treating MB patients until skin smear negativity. The bacteriological index (BI) is one of the tools for assessing the efficacy of a treatment regimen in leprosy. However, the BI cannot differentiate between dead and viable organisms. The clearance of dead bacilli from skin tissue continues at about 0.6 to 1.0 unit of BI per year, even after MDT is discontinued.*

Q.12

What should be done if a PB patient, 9 months after starting treatment, has not taken 6 monthly doses of MDT or if an MB patient has not completed 24 monthly doses of MDT 36 months after starting treatment?

A: *Such situations should be exceptional or rare in a good programme which is providing MDT services without any inconvenience to the patient, keeping the patient fully informed of the importance of regular drug intake. However, if a patient is unable to complete the required number of doses in time, for any reason, the treatment regimen should be continued from where it was left off and the full course completed. Do not restart the regimen from the beginning. If the patient is properly explained at the time of diagnosis, in most cases it is possible to let the patient take full responsibility for his/her treatment.*

What do you mean by a defaulter? What do you do if a defaulter comes back for treatment?

A: *A defaulter is a patient who has not collected treatment for 12 consecutive months. Once a patient has been categorized as a defaulter this patient should be removed from the register. Before doing so, adequate efforts should be made to trace and persuade each defaulter to return for assessment and treatment.*

A defaulter who returns to the health centre for treatment and shows one or more of the following signs should be given a new course of MDT:

(i) reddish and/or elevated skin lesions; (ii) appearance of new skin lesions since last examination; (iii) new nerve involvement since last examination; (iv) lepromatous nodules; (v) signs of erythema nodosum leprosum (ENL) or reversal reaction.

Q.14

Is it necessary to give MDT to MB and PB patients who were on dapsone monotherapy and are now bacteriologically and clinically inactive?

A: The reports available from routine control programmes suggest that a small proportion of patients who had several years of dapsone monotherapy are relapsing, especially MB leprosy patients. Wherever resources permit, such patients should be treated with WHO/MDT for two years provided this activity does not interfere with other activities and such patients are not re-registered as new cases.

Q.15

Does MDT help to bring about skin smear negativity earlier than with dapsone monotherapy?

A: The main function of MDT is to kill all viable organisms, which can be achieved in a relatively short period. The clearance of dead bacilli depends largely on the individual's immune response which, especially in individuals suffering from MB leprosy, is defective. The results of several large-scale, long-term field trials show that the rate of clearance of dead bacilli is about 0.6 to 1.0 logs per year and is not enhanced by MDT.

Q.16

Is the threat of rifampicin-resistant leprosy a serious problem?

A: *There are a few isolated reports of rifampicin-resistant leprosy; these are mainly from areas where rifampicin was given as monotherapy, either alone or in combination with dapsone, to dapsone-resistant patients. At the moment, the problem of rifampicin-resistant leprosy is not a serious one; however, selective noncompliance with dapsone and/or clofazimine by patients may facilitate selection of rifampicin-resistant strains.*

Q.17

Does MDT expose patients to a higher risk of serious side-effects?

A: *When more than one drug is used, naturally there is a risk of side-effects from each of the drugs used in the combination. However, in practice, the side-effects reported from the use of MDT in several hundreds of thousands of patients around the world show that most of them are mild and major side-effects are rare.*

Does MDT increase the frequency and severity of lepra reactions?

A: *The evidence available shows that there is a significant reduction in the frequency and severity of ENL (Type 2) reactions in MB leprosy patients on MDT. It is possible that this is attributable to the anti-inflammatory effect of clofazimine. On the other hand, there seems to be a higher reporting of reversal reactions (Type 1) in MB leprosy patients in the first year of MDT which then gradually declines. However, it is not clear whether this is because of more stringent follow-up of patients, which detects mild reactions that would otherwise have been missed, or whether there is a real increase in the incidence of reversal reactions.*

Q.19

What kind of harm can be done if patients are irregular in taking MDT?

A: *The most important harm that can be done if patients do not take MDT regularly is that the cure will be delayed or incomplete. The disease activity will progress and the patient may develop serious disabilities and deformities. These patients will become a source of infection to the community, in addition to perpetuating stigma generated by unsightly deformities. More seriously, if the irregularity is selective to one or the other drug in MDT then there is a possibility of drug resistance to multiple drugs. However, the WHO-recommended MDT regimens have been shown to be robust i.e. even if taken irregularly, they have benefited patients.*

What is to be done if leprosy programmes run short of one or more drugs used in MDT?

A: *Hopefully such a situation would be exceptional and one that should be avoided at all costs. There are practically no alternatives available in such situations. It is important that project managers at all levels keep a close watch on their drug supply position and take timely action. The principle of using three drugs in MB leprosy and two drugs in PB leprosy should be adhered to under all circumstances. Shortage of one or more of the required drugs can be avoided by using the WHO recommended blister packs. Each pack contains all the necessary drugs for four weeks treatment, and are individually marked with their own expiry date.*

What treatment can be given to patients who do not tolerate MDT due to adverse reactions or contra-indications?

A: *It is very important to establish conclusively that the adverse reactions seen are due to the anti-leprosy drugs. Once this is established, other new anti-leprosy drugs can be tried. In place of rifampicin one could use ofloxacin 400 mg daily and minocycline 100 mg daily (or clarithromycin 500 mg daily) given along with the daily administration of clofazimine 50 mg for the first 6 months. This is to be followed by daily administration of clofazimine 50 mg, ofloxacin 400 mg or minocycline 100 mg for the next 18 months. This regimen should be administered under direct supervision in a referral centre.*

If the toxic effects of dapsone are severe in PB patients, then dapsone may be substituted by clofazimine in the same dosage as that used for MB patients but for 6 months. In MB patients, dapsone should be stopped and treatment continued with rifampicin and clofazimine in the standard dosage. When clofazimine is unacceptable to the patient, ofloxacin 400 mg daily or minocycline 100 mg daily may be substituted in place of the clofazimine component of the standard MDT regimen, and should be given under supervision in a referral centre.

How should patients who refuse to take clofazimine be managed?

A: *The experience gained so far shows that the number of patients who refuse to take clofazimine is not very large. However, in certain populations, this can be a serious problem. It may be worthwhile spending some time in educating the patient about the advantage of taking clofazimine, in particular the reversible nature of the discolouration produced by the drug. In most cases this approach should be sufficient to encourage the patient to continue with clofazimine. In exceptional cases, ofloxacin 400 mg or minocycline 100 mg daily may be used under supervision in place of clofazimine.*

Q.23

How serious are the side-effects of clofazimine, such as discolouration and ichthyosis and how can they be managed?

A: *The discolouration caused by clofazimine usually does not cause any serious problem, except for the fact that it may be cosmetically unacceptable to some patients. The accompanying ichthyosis may predispose to certain dermatitis, especially in dry climatic conditions. This can be reduced by moistening the skin, followed by regular application of vaseline or vegetable oils and avoidance of unnecessary exposure to bright sunlight.*

Q.24

How long does it take to reverse the discolouration caused by clofazimine?

A: *The discolouration caused by clofazimine is completely reversible. It starts to appear by the third month of MDT and reaches its maximum intensity by the end of the first year. After discontinuation of MDT, the discolouration starts to diminish noticeably in six months and the skin returns to its normal colour at the end of one year after stopping MDT.*

Q.25

Will the widespread use of rifampicin for treating tuberculosis (TB) and sexually transmitted diseases (STD) have any effect on the use of MDT in leprosy patients?

A: It is possible that if a leprosy patient with tuberculosis is treated for tuberculosis with a rifampicin-containing anti-tubercular regimen, he/she may run the risk of developing rifampicin-resistant leprosy. Hence, the need to treat both diseases simultaneously. Use of rifampicin for STD for very short periods may have no significant effect on the emergence of rifampicin-resistant M. leprae.

Is MDT contra-indicated in patients suffering from tuberculosis?

A: MDT is not contra-indicated in patients suffering from tuberculosis. It must be remembered that tuberculosis is a serious disease and must be treated promptly. WHO/MDT for leprosy is not adequate for the treatment of tuberculosis and therefore an appropriate anti-tubercular regimen should be given, in addition to the antileprosy MDT, to patients who are diagnosed to have both leprosy and tuberculosis - except if daily rifampicin is part of the anti-tuberculosis treatment, in which case there is no need to administer monthly rifampicin as part of the leprosy MDT.

Q.27

Is MDT contra-indicated in patients suffering from human immunodeficiency virus (HIV) infection?

A: *MDT is not contra-indicated in patients suffering from HIV infection. The management of leprosy patients infected with HIV is the same as that of any other patient. The response of such patients to MDT is similar to that of any other leprosy patient so management, including treatment of reactions, does not require modification.*

Q.28

Is MDT safe during pregnancy and lactation?

A: *Since leprosy is exacerbated during pregnancy it is important that MDT be continued. All evidence so far indicates that MDT is safe during pregnancy. A small quantity of anti-leprosy drugs are excreted through breast milk but there is no report of adverse reaction as a result of this except for mild discolouration of the infant due to clofazimine.*

Q.29

A small number of patients do not show any clinical or bacteriological improvement with MDT. How should these patients be managed?

A: *There may be several reasons for such occurrences in a small number of patients. The two most important reasons may be poor drug compliance and other concomitant, debilitating, intercurrent infection. The problem of poor compliance may be solved by supervised drug administration and health education. The problem of concomitant, intercurrent infection needs thorough investigation (including, where indicated, tests for HIV infection) and appropriate management. If these measures fail, it may be necessary to seek expert opinion.*

Is it necessary to give MDT cover to patients who have to receive steroids (e.g. for late reversal reaction or other medical conditions) even after successful completion of the scheduled course of MDT?

A: *The risk of possible endogenous reactivation is probably higher during the initial few years after completion of chemotherapy in a small number of patients. Immunosuppressive drugs, like corticosteroids, are known to accelerate the multiplication of organisms located in dormant foci and cause disseminated reactivation; for example, in TB. Whenever possible, 50 mg of clofazimine daily is started as a prophylactic measure if the duration of steroid therapy is expected to exceed 4 months, and should be continued until the course of steroids is complete. However, these patients should not be re-entered into the case registry.*

After patients have stopped treatment, how does one recognize relapse? How can relapse be distinguished from the various types of reactions?

A: Relapse, in MB leprosy, is defined as the multiplication of M. leprae, suspected by the marked increase (at least 2+ over the previous value) in the BI at any single site, usually with evidence of clinical deterioration (new skin patches or nodules and/or new nerve damage). This can be confirmed in most cases by the growth of M. leprae in the mouse footpad system. Recognition of relapse in paucibacillary leprosy is somewhat difficult as it is hard to distinguish it from reversal reaction. In theory, a therapeutic test with corticosteroids may be able to distinguish between these two phenomena: definite improvement within four weeks of corticosteroid therapy denoting reversal reaction, and non-response to corticosteroids during the same period favouring the diagnosis of clinical relapse.

Q.32

In some control programmes, after completion of MDT, patients continue with a single drug, usually dapsone, for various lengths of time. Is it necessary?

A: *The continuation of dapsone monotherapy after a course of MDT is totally unnecessary. Some control programmes may be using this to ensure regular follow-up; to satisfy patients who are not willing to discontinue treatment; or in situations where the physician may not be convinced of the efficacy of MDT.*

Whatever the reason, this approach puts an unnecessary burden on the patient and on the field workers and cannot be recommended.

Q.33

Are skin smears a prerequisite for starting a patient on MDT?

A: *No, skin smears are not a prerequisite for starting a patient on MDT. The clinical system of classification for the purpose of treatment includes the use of numbers of skin lesions and nerves involved as the basis for grouping the leprosy patients into MB and PB. If in doubt, the patient should be treated with MB regimen.*

How often should skin smears be taken during and after the completion of MDT?

A: *If reliable facilities for skin smears are available, then ideally all patients should have one examination at the start of treatment. This is to prevent an MB case being treated as PB. With fixed-duration treatment regimens, skin smears are not needed either to stop treatment or as a routine measure for follow-up of patients after completion of treatment. In patients where clinical deterioration/relapse is suspected, skin smears should be taken from the most active sites.*

In view of the increasing prevalence of human immunodeficiency viruses (HIV) and hepatitis B infections in many countries where leprosy remains endemic, the number of skin-smear sites and the frequency of smear collection should be limited to a minimum. Remember that all skin-piercing procedures have the potential risk of transmitting HIV and hepatitis infections.

Q.35

Is post-MDT surveillance of patients essential?

A: *Because the risk of relapses after completion of the WHO MDT regimens has been negligible, it is no longer necessary to continue routine post-MDT surveillance. Instead, patients should be taught at the time of release from treatment to recognize early signs of possible relapses or reactions and to report promptly for treatment.*

Q.36

It is said that almost all the bacilli seen in skin smears after MDT are dead bacilli. Is there any way to accelerate their removal?

A: *There are some reports that immunotherapy using M. leprae or other mycobacteria-derived vaccines may be useful in accelerating the clearance of dead bacilli from the tissues. However, more research is needed before this approach can be recommended for use in routine leprosy control programmes.*

Q.37

Does the presence of dead bacilli in the skin and other tissues cause the patient any problems?

A: *In most patients the presence of dead bacilli in the skin and other tissues does not cause any problem, and the dead organisms are gradually cleared by the phagocytic system of the body. However, in a very small proportion of patients, the antigens from dead bacilli can provoke immunological reactions, such as reversal reaction, causing serious nerve damage and subsequent disabilities.*

Q.38

What is the role of WHO in ensuring that MDT drugs are freely available for all leprosy patients in need?

A: *Since 1995, WHO is supplying MDT in blister packs to most of the endemic countries. These are now available as blister packs for MB-adult, MB-child, PB-adult and PB-child. In this way WHO is making sure that every patient in the world has access to the best possible quality of MDT drugs, totally free of cost. In addition, the use of MDT in blister packs will ensure safe storage and prevent possible misuse of rifampicin.*





